

REMARKS

A. The Status of the Claims and the Amendments

Claims 1-115, 132-137, 142-145, 152-159, 161-163, 167, and 175-177 have been previously canceled without prejudice. Claims 180-250 were previously withdrawn as claims drawn to non-elected species. The Applicant is pleased to acknowledge the fact that in view of the previous argument, the Examiner has agreed that claims 226-250 should not have been withdrawn from consideration, and that, accordingly, claims 226-250 have been re-instated for current consideration.

By the present amendment, each of claims 116, 164, and 226 has been amended to claim the invention with greater particularity and specificity. Specifically, some matter previously introduced and objected to by the Examiner as allegedly a "new matter" has been deleted. No new matter has been introduced in the amendments. The limitation reciting the proviso that "between about 1 and 10 mol. per cent of said lipids comprise negatively charged lipids" added to claims 116 and 226 is disclosed in paragraph [0066] on page 6 of the originally filed application (see document US 2001/0051131). Accordingly, entry of the amendment is respectfully requested.

Claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, and 178-267 are now pending, of which claims 180-225 remain withdrawn as claims drawn to non-elected species, and claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, 178, 179, and 226-267 are currently under consideration.

B. Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 226-250 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the

application was filed, had possession of the claimed invention (the written description requirement) (last paragraph on page 4 of the Office Action). More specifically, the Examiner has stated that the limitation "delivering said bioactive agent from the vasculature through the vessel wall and into said selected tissue" is not disclosed in the original specification, and thus constitutes new matter.

The Applicant disagrees with such characterization. The original specification does disclose the above-mentioned limitation. However, in order to facilitate the process of prosecution of this application, claim 226 has been amended and the limitation "from the vasculature through the vessel wall" have been deleted.

Therefore, the rejection has become moot. Accordingly, reconsideration and withdrawal of the rejection of claims 226-250 under 35 U.S.C. § 112, first paragraph, are requested.

C. Rejections Under 35 U.S.C. § 103(a)

Claims 116-125, 129-131, 138-141, 146-151, 160, 164-166, 168-174, 178, 179, 226-230, and 232-250 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,695,460 to Siegel et al. ("Siegel"), in view of U.S. Patent No. 5,334,381 to Unger ("Unger"), and further in view of U.S. Patent No. 5,648,098 to Porter ("Porter") (last paragraph on page 6 of the Office Action). In addition, claims 126-128, 231, and 251-267 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Siegel, in view of Unger, further in view of Porter, and further in view of U.S. Patent No. 5,393,530 to Schneider et al. ("Schneider") (the paragraph bridging pages 17 and 18 of the Office Action). These rejections are respectfully traversed.

The standard that has to be satisfied in order to make a valid rejection based on a *prima facie* case of obviousness was described in a response to a previous Office Action.

This standard has been modified recently by the recent Supreme Court decision in the *KSR International v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ 2d. 1385 (2007), and there is no longer a strict requirement to satisfy the old “teaching-suggestion-motivation” standard to show obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references. The Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness either under the old standard or according to the modified standard.

More specifically, neither Siegel nor Porter provide the disclosure that is commensurate with the scope of the present invention as claimed in claims 116, 164, and 226. Indeed, the instant claims at issue recite methods for **delivering** of an agent to a selected tissue. To that end, the instant claims require that not just any amount of ultrasound be delivered, but an amount sufficient to produce cavitating and/or rupturing the vesicles, as in claims 116 and 226, or sufficient to activate the acoustically active composition, as in claim 164.

Siegel fails to describe or even to suggest the application of ultrasound in an amount **sufficient to achieve efficient drug delivery**, because Siegel is not concerned with delivering an active agent to selected tissue. In contrast, the methods described by Siegel are directed solely to dissolving arterial thrombi. Accordingly, Siegel teaches that an echo contrast agent is administered to a patient (e.g., by injection), optionally together with a thrombolytic agent. The process is finished when ultrasound is applied. As a result of the combined contrast agent/ultrasound application, “substantial dissolution of

the thrombosis without the need for the introduction of thrombolytic agents” can be achieved (col. 5, lines 26-28), but there is nothing in Siegel linking the use of ultrasound to the delivery of an active agent to selected tissue. Siegel attributes usefulness of his method to the increased cavitation of vascular fluid surrounding the thrombosis. (col. 5, line 66 to col. 6, line 3). In other words, the motivation one skilled in the art can get from Siegel is as to the potential improvement of thrombolysis, not as to delivering an active agent to selected tissue.

The Examiner may be correct in observing that Siegel possibly teaches that optional use of a thrombolytic agent, in connection with administering ultrasound and a contrast agent, can improve thrombolysis; however, there is nothing in Siegel describing **delivery** of the thrombolytic agent to a selected tissue, much less that ultrasound can enhance such a delivery. In sum, Siegel contains neither explicit disclosure nor even an implied suggestion as to the use of ultrasound for augmenting **delivery** of an active agent to a tissue.

In addition, the Applicant respectfully reminds that Siegel only teaches a method of thrombolysis in which preferably the frequency between 24 and 53 KHz is used, particularly 25-39 KHz. No frequency above 243 KHz, including frequencies between 750 kHz to 3 MHz, required by the instant claims 116, 164, and 226, is described or suggested in Siegel. In addition, as previously discussed, Siegel teaches away from using high frequencies. Indeed, Siegel states (col. 5, lines 30-35) that

“when ultrasound is applied at a lower, rather than a higher frequency, the effectiveness of the method is markedly enhanced. More particularly, when ultrasound is applied at less than about 100 kHz, and even more particularly, between approximately 25 kHz and approximately 53 kHz, the dissolution of thrombi is most significant.”

Indeed, Siegel further indicates that no good results were achieved when higher frequencies of ultrasound were used (col. 7, Example III, and compare the results shown in Table 14, at 105.4 kHz, with those in Table 10, at 24.8 kHz).

Both under the teaching-suggestion-motivation test and the more nuanced KSR approach, showing of the likelihood of success is required. The Applicant submits that the Examiner has ignored this requirement and completely disregarded very clear teachings of Siegel with regard to the frequency range to be used. The Applicant respectfully submits it was improper not to take into account the fact that Siegel teaches away from using high frequencies and urges the Examiner to reconsider this point. The Applicant is confident that if the Examiner agrees to do so, she would see that Siegel, alone or in combinations with any other reference, cannot be used for making a good *prima facie* case of obviousness.

To cure the deficiencies of Siegel, particularly those related to the frequency range issue, the Examiner proposes to combine Siegel, Unger and Porter, because Porter mentions a possibility of using the frequency up to several megahertz.

Although Porter mentions briefly the application of ultrasound having higher frequencies, the Applicant respectfully submits that it would be improper to combine Porter and Siegel, because their teachings are contradictory, or at least inconsistent. As discussed above, Siegel explicitly teaches away from making such a combination. It is, however, well established that a reference must be considered in its entirety, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F. 2d 1540 (Fed. Cir. 1983).

Thus, a rejection combining Porter with Siegel can be only made using hindsight reasoning, with a rationale that comes from the application itself, not from any motivation taught by the prior art. Such rejections are clearly improper and absent the

teachings of the instant application, one of ordinary skill in the art would have had no reason to make such a combination.

Therefore, it is submitted that one skilled in the art would not be motivated to modify the teachings of Siegel et al. towards the increase in frequency to 750 KHz or higher, because the teachings of Siegel et al. suggest that such modification will lead to worse results.

In addition, each of claims 116 and 226 has been amended and each now requires that "between about 1 and 10 mol. per cent of said lipids comprise negatively charged lipids." Such limitation is neither disclosed nor suggested in any of Siegel, Unger, or Porter or any combination thereof. It is submitted that this limitation alone overcomes the obviousness rejection.

Moreover, like Siegel, Porter is directed to thrombolytic therapy, not to the drug delivery, and it appears that the Examiner agrees (see, page 10, last paragraph of the Office Action). Applicant respectfully emphasizes that Porter's disclosure is still directed to the treating thrombosis, not to the delivery of a bioactive agent, as instantly claimed. Like Siegel, Porter contains no teaching or suggestion that his methods may be used to enhance the delivery of the bioactive agent.

In view of the foregoing it is submitted that each of claims 116, 164, and 226 is patentably distinguishable over Siegel et al. in view of Porter. Each of claims 117-125, 129-131, 138-141, 146-151, 160, 165, 166, 168-174, 178, 179, and 226-267 depends, directly or indirectly either on claim 116, claim 164, or claim 226 and is considered patentable for at least the same reason. Therefore, reconsideration and withdrawal of the rejection of claims 116-125, 129-131, 138-141, 146-151, 160, 164-166, 168-174, 178, 179, and 226-267 are respectfully requested.

With respect to the obviousness rejection of claims 126-128, 231, and 251-267, these claims depend on either claim 116 (i.e., claims 126-128) or on claim 226 (i.e., claims 231, and 251-267). As shown above, each of claims 116 and 226 is patentable over the combination of Siegel, Unger and Porter. The Examiner has correctly indicated that this combination fails to teach that the liposome can comprise phospholipids, such as dipalmitoylphosphatidylethanolamine or dipalmitoylphosphatidic acid. To cure this deficiency, the Examiner proposes to combine Siegel, Unger, and Porter with Schneider.

However, Schneider does not help at all to eliminate of problem of incompatibility of the teachings of Siegel and Porter, as discussed above. Even if the teachings of Schneider were otherwise applicable, Schneider cannot provide the motivation of using higher frequencies, for example. All Schneider is useful for is to provide the disclosure of certain phospholipid. Schneider does not and cannot eliminate all other deficiencies of Siegel discussed above.

Accordingly, each of claims 116, and 226 is patentably distinguishable over Siegel, in view of Unger, and further in view of Porter, and further in view of Schneider. Each of claims 126-128, 231, and 251-267 depends, directly or indirectly either on claim 116 or claim 226 and is considered patentable for at least the same reason. Therefore, reconsideration and withdrawal of the rejection of claims 126-128, 231, and 251-267 are respectfully requested.

In re Application of:
Evan C. Unger
Application No.: 09/413,110
Filed: October 6, 1999
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PATENT
Attorney Docket No. IMARX1110


CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge \$525.00 as payment for the Petition for Three-Month Extension of Time fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-referenced Attorney docket number.

Respectfully submitted,

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